one fully variable codon and one less variable codon, the position of the less variable codon varying so that said plurality collectively scan also positions other than said first fixed position, said less variable codon encoding the second position of each peptide.

each library being a separately screenable and distinct physical entity from the other libraries of the panel.

36. The panel of claim 35 in which, in a given library, the first and second positions are amino acids belonging to one and only one of the following groups:

1	W	TGG
2	F, Y	T(T,A)T
3	P	CCT
4	H	CAT
5	D, E	GAX
6	K, R	A(G,A)A
7	N	AAT
8	Q	CAA
9	L, I, V	(G,A,C)TT
10	M	ATG
11	S, T	A(G,C)T
12	A, G	G(G,C)T
13	C	TGT

37. The panel of claim 36 in which, in a given library, the first fixed position belongs to one and only one of groups 1-7 and 13.

38. The panel of claim 31 wherein the overall diversity of the panel at the fixed position of the peptides is the same as the overall diversity of the panel at each of the other positions of the peptides.--

REMARKS

1. General Matters

1.1. Claims 21-23 were examined, and claims 1-20 and 24 were restricted out. However, the November 29, 1999 action overlooked the second preliminary amendment filed September 29. This amendment cancelled claims 1-20 and 24, and added new claims

25-30.

Enclosed herewith are (1) a courtesy copy of the amendment and (2) a postcard receipt for the amendment.

Naturally, since claims 25-30 were pending, but not examined, the next action on this case, if a rejection, cannot be made final.

1.2. As a result of the current amendment, claim 21 has been replaced by new claim 31, and claim 23 (which had been dependent on 21) by independent claim 32. Conforming amendments have been made to other claims.

1.3. With regard to the IDS filed October 21, 1999 (not 1998 as stated in the OA), there is an exception to rule 1.98(a)(2) which is spelled out in rule 1.98(d):

> A copy of any patent, publication or other information listed in an information disclosure statement is not required to be provided if it was previously cited by or submitted to the Office in a prior application, provided that the prior application is properly identified in the statement and relied upon for an earlier filing date under 35 U.S.C. 120.

This rule plainly applies to the reference listings which were from Serial No. 08/740,671 (Fowlkes4).

There are two sheets of references (one beginning with Ladner '409, the other with Ellman '514) which were new to this case, and hence copies were required. However, we definitely filed those copies; our receipt is attached.

The failure to consider the IDS is a further reason why the next action cannot be made final.

<u>2. Prior Art Issues</u>

The present invention is directed to <u>structured</u> <u>panels</u> of

combinatorial peptide libraries. A "structured panel" may present, collectively, the same peptides as a simple combinatorial library (e.g., all hexapeptides formable from the 20 genetically encoded amino acids), the difference is that instead of presenting them as a simple mixture, it presents them as a collection of <u>separately screenable</u> libraries, each offering only a subset of the diversity provided by the panel as a whole.

The Examiner's attention is directed to the definitions at page 8, lines 9-12 and at page 9, line 33 to page 10, line 8:

> A biased combinatorial library is one in which, at one or more positions in the library member, only one of the possible basic elements is allowed for all members of the library, i.e., <u>the biased positions are invariant</u>.
>
> A "panel of combinatorial libraries" is a collection of different (although possibly overlapping) and separately screenable simple or composite combinatorial libraries. A "panel" differs from a composite library in that the component simple libraries have not been mixed together, that is, they may still be <u>screened separately</u>.
>
> A "structural panel" is a panel as defined above where there is some structural relationship between the member libraries. For example, one could have a panel of 20 different biased peptide libraries where, in each library, the middle residue is held constant as a given amino acid, but, in each library the constant residue is different, so, <u>collectively, all 20 possible genetically encoded amino acids are explored by the panel</u>. [emphasis added]

The advantage of this structure is that it allows one to more readily find binding peptides if a particular amino acid at the biased position is necessary for binding, see page 26, line 17 to 29 and page 27, line 24. Even if the requirement were not absolute, the structuring facilitates the elucidation of the sequence-binding activity relationships.

New claim 31 is directed to a structured panel which has a single and fixed constant residue position (bias position) for all of its component libraries. Moreover, claim 31 requires that the bias position must fall either at least five residues from both ends of the peptide (per page 25, lines 36-37) or in the "middle 50%" of the peptides.

Since claim 31 is in "closed" form ("consisting of...) the panel cannot include any biased libraries in which the bias position is outside the "middle 50%". It also cannot include any unbiased (completely variable) peptide libraries.

By keeping the biased position away from the ends, applicants make it easier to identify binding peptides if (1) the bias AA is required at the bias position for activity, and (2) one needs particular flanking residues to assure it is properly positioned. See page 26, lines 2-7.

At page 10, lines 16-20, the specification refers to a second library embodiment:

> One may have structured panels of libraries in which one may define subpanels, too. For example, in one subpanel, the middle residue AA_1 may be the same for all libraries, but the libraries also have a constant residue AA_2 which is scanned through all other residue positions.

The meaning of "scanned" is explained at page 10, lines 9-15:

> A "scanning residue library" refers to the preparation of panel of biased combinatorial peptide libraries such that the position of the constant residue shifts from one library to the next. For example, in library 1, residue 1 is held constant as a particular residue AA, in library, residue 2 is, and so forth through two or more (usually all) positions of the peptide.

At page 27, line 25 to page 28, line 3, there is reference to a <u>simple library</u> (not a panel) biased at two positions.

Subsequently, at page 28, lines 4-16, the applicants discussed a structured panel of parallel biased libraries of 11 a.a. peptides, with <u>two scanning</u> constant positions (resulting in 44,000 parallel libraries), and a more modest structured panel in which one constant position is fixed (at position 6), and the other scans (resulting in 4,000 libraries).

New claim 32 is directed to a structured panel in which there are two, and only two, constant positions in any given library, where one position is fixed at the same location for all libraries (and is centrally located), and the other constant positions "scans" the remainder of the peptide.

New claim 33 is directed to the variant of claim 32, discussed at page 28, in which the "constant" residue is replaced by a "lower variability" biased residue, such as one allowing up to 3 different amino acids at the position in question (cp. claim 34). (The "3" is based on group 9 on page 28.)

Claim 34 is based on e.g., page 26, lines 22-23 and page 27, lines 14-17.

Claim 35 is directed to the variant of page 29.

Claim 36 further limits the choice of the central constant residue in accordance with the teachings at page 31, lines 10-20.

We turn now to the specific rejections.

2.1. Claims 21-23 stand rejected as anticipated by Pinilla (1995).

The Examiner directs our attention to the positional scanning libraries of Pinilla Table 2. These are discussed at page 225: "PS-SCLs are composed of individual position SCLs in which a single position is defined with a single amino acid, while the remained positions are composed of mixtures of amino acids. The defined position is walked through the entire sequence of the PS-SCL."

The Examiner points out that in some of Pinilla's individual position SCLs, the constant residue will be in the middle 50%. For example, in the case of the decapeptide of Table 1, 50% of

10 is 5, so the middle 50% are 4-7, and the libraries with O_4 through O_7 in combination could be considered a structured panel according to our claim 21.

Claim 21 is replaced by new claim 31, which is in closed format, and therefore excludes those libraries of the Pinilla Table 2 PS-SCL panel in which the constant position is outside the middle 50% and less than 5 a.a. from one end of the peptide.

Hence, claim 31 is not anticipated by the Pinilla panel.

Claim 23 is replaced by new claim 32, directed to a structured panel in which one constant position is fixed and the other scans. The cited Pinilla panel has a single constant position, which is a scanning position. None of the Pinilla libraries would include a library like O_1-X-X-X-X-O_2-X-X-X-X-X, where O_1 is a scanning residue and O_2 a fixed residue, both constant. Hence, Pinilla does not anticipate claim 32.

We do <u>not</u> agree with the Examiner's further argument on page 8, lines 7-14, which is apparently aimed at the one fixed/one scanning embodiment of claim 23 (now replaced by 32). Pinilla's decapeptide panel is composed of 200 separate libraries (separately testable entities). In each, one of the 20 a.a. is the constant residue, in one of ten positions (20x10=200). We would prepare four subpanels (with positions 4, 5, 6 and 7 as the fixed residue), each of 20 a.a. (one for each possible fixed residue) x20 a.a. (one for each possible scanning residue)x9 (one for each scanning position) for a total of 14,400 independently testable libraries (cp. discussion at our page 28, lines 4-12).

The different structuring of the libraries is relevant, even though both panels are ultimately composed of the same peptides.

Neither is claim 32 anticipated by Pinilla's dual fixed SCLs (page 227, col. 2, O_1O_2XXXX), as, while there are two constant positions, they are fixed for all libraries of Pinilla's panel.

2.2. Claims 21-23 are rejected as anticipated by Huffman p. 14-15 (OA §7). This discloses panels of libraries with one to five (01 to 05) constant positions.

The first panel prepared is, e.g., O^1XXXXX, and is used to determine the optimal residue 1. The next panel is O^1O^2XXXX, then $O^1O^2O^3XXX$, and so on. Huffman also discloses, as an alternative, progressive optimization from the C-terminal.

Neither the O^1XXXXX nor the $XXXXXO^6$ panels anticipate claim 31 (the successor to 21), as the bias position in Huffman is at either end of the peptide, not more centrally located as required by claim 31. The other Huffman panels have more than one bias position, and hence do not anticipate, claim 31.

Claim 32, the successor to claim 23, is not anticipated by Huffman O^1O^2XXXX or $XXXXO^5O^6$ panels, both because the two bias positions in Huffman's panels are both fixed, and because they are not centrally located as at least one of the bias positions in claim 32 must be.

Huffman also discloses the panel O^1XO^3XXX, but this library does not anticipate claim 32 because both bias positions are fixed positions.

If Huffman's sequences 7 and 13 were deemed subpanels of a single panel, then one bias position is fixed, and the other shifts, but the fixed position is at the N-terminal and the scanning is incomplete.

2.3. Claims 21-23 are again rejected over Pinilla (OA §8), but this time assuming that "having one or two constant residues" is open, i.e., could encompass more than two constant residues. New claims 31 and 32 limit the number of constant residues in the recited libraries to one and two respectively.

2.4. Claim 23 is rejected as anticipated by Spatola (1996) (OA §9). Spatola Table 1 presents a panel of 48 cyclic pentapeptide libraries. Residue 5 is Asp in all of the libraries. The Examiner points out that since the peptides are cyclic, the limitation "middle 50%" is meaningless. L1-L2 hold AA3 constant, L15-L24 hold AA2 constant, and so forth. Thus, there is one scanning residue, which scans positions 1-4, and corresponds to the "second position" of claim 23 (or 32).

However, Spatola AA5 does not correspond to the "first position" of claim 23, since our base claim 21 requires that this AA "is not the same in all libraries of said panel".

2.5. Claims 21-22 are rejected as anticipated by Cantley col. 10, line 41 to col. 12, line 1. Cantley discloses a library of the form

$$(Xaa)_{1-10}\text{-}Zaa\text{-}(Xaa)_{1-10} \quad \text{(SEQ ID NO:1)}$$

where Xaa is any amino acid, and at least some Xaa are degenerate.

Please note that while Zaa may be Ser, Thr or Tyr, it must be "non-degenerate", see col. 10, line 46. Hence, Cantley's sequence 1 does not anticipate claim 31 (replacing 21) because 31 requires a <u>panel</u> of libraries in which there is a library-to-library variation of the residue corresponding to Cantley's Zaa.

Table 9 shows a nonapeptide library in which AA_5=Y and the other residues are partially degenerate (2-6 possibilities each).

Claim 23 is rejected as anticipated by Cantley based on the erroneous "same peptide" argument discussed previously. (OA page 10, lines 1-6).

2.6. Claims 21-23 are rejected as anticipated by Holmes Fig. 7 (OA §12). According to the Examiner, this describes a panel of 36 biased cyclic hexapeptide libraries of 20 amino acids each, with one fixed constant position and one scanning constant position.

The patent is rather confusing; its emphasis is on efficient panel synthesis. Col. 11 and Fig. 1 describe a simple panel of seven heptapeptide libraries (140 peptides, 134 unique) with one scanning <u>variable</u> residue. At col. 12, we have a panel with two <u>tandemly</u> scanning <u>adjacent variable</u> residues. This adds five panels of 20 libraries each.

Cyclic polymers are discussed beginning on col. 14. It appears that in Fig. 7C, only the X residue 18 a variable residue, while the A (tether) residue and the residues numbered 1-7 are constant across the entire panel. Residue A is not a

"first position" residue within the meaning of claim 23, because it never varies. Residue X scans, but it is variable, not constant. Residues 1-7 are constant, but scrambled in location and sometimes omitted (for exampled, in the first library, there is no "6" or "7", and in the second, no "1" or "6"). So Holmes is far removed from claims 21-23.

2.7. The claims are also rejected as obvious, as follows: (1) claim 23 over Holmes Fig. 8, (2) claims 21-22 as obvious over Pinilla in view of Huffman, and (3) claim 23 as obvious over Pinilla in view of Spatola, Lebl or Holmes. Only Lebl is new, and is cited for teaching (on page 192) linking active motifs with a variable length/variable composition linker. While one can argue that inbetween a first fixed constant position and a second scanning constant position one has a variable linker, the constant positions, by themselves, are <u>not</u> active subunits. What Lebl has in mind is linking two active oligopeptides by a variable length randomized linker. That is different from what is claimed here. The combined art does not disclose or suggest the claimed subject matter.

<u>3. Definiteness</u>

1. The Examiner questions how "middle 50%" is to be determined if the peptide is an odd length. Let us say it is an 11-mer. 50% of 11 is 5.5. Half that is 2.75. The middle position is 6, so the middle 50 is position (6-2.75=) 3.25 to 6+2.75=8.75. Since a fractional position is meaningless, the "middle 50%" are positions 4 to 8. The term is not indefinite.

In view of the problem of determining "middle 50%" when the peptides are cyclic, the claims are now limited to linear peptides.

2. The terms "having" is no longer used in the claims.

<u>4. Enablement</u>

The Examiner questions enablement for a library of 30 a.a.

peptides, as the potential max of 20^{30} peptides would have a mass on the order of $6x10^{10}$ kg if all positions were varied simultaneously.

The claims no longer require that all 20 genetically encoded amino acids appears at each position. Hence, a 30 amino acid peptide library could conceivably present just 2^{30} (10^{9}) different sequences.

Moreover, it is clear that we must distinguish between (1) positions which are constant at the library level and variable at the panel level, and (2) positions which are constant even at the panel level. A long peptide is likely to have more of (2) than would a short peptide.

In our 11-mer libraries, each with two residues constant (type 1), each library would have 20^{9} (nearly 10^{12}) different peptides, and the panel as a whole would offer 20^{11} different peptides. We have made and screened $X_{10}C$ libraries with 20^{10} ($\tilde{}10^{13}$) different peptides. page 60, Table A-1 refers to a "random X_{12}" library, which would be 20^{12} ($\tilde{}4x10^{15}$) different sequences. Page 57, lines 14-15 asserts that it is technically feasible to make libraries with random stretches of 25 residues".

Clearly, there is a relationship between the diversity of the library, and the mass thereof. Screening a large mass can pose technical problems. However, as a matter of law, it is improper to construe a claim so as to read it on an impossible embodiment, which the person skilled in the art would never dream of making, and then use that reading to justify invalidating the claim. See <u>In re Skrivan</u>, 127 USPQ 202 (CCPA 1960).

Cantley claim 4 could cover a library of 20^{20} peptides. In Holmes claim 1, there is no upper limit on N, the peptide length.

<u>5. Utility (35 USC §101)</u>

The Examiner asserts that the claimed combinatorial libraries lack a practical utility because (1) they comprise "a collection of compounds that (as a whole) have no known

biological activity, but that are merely drug or ligand candidates", and (2) even if some of the compounds have binding affinity for a target protein, that does not mean that pharmacological activity must necessarily follow.

The Examiner concedes that "research tools", such as a gas chromatograph, have a practical utility in identifying useful compounds, but distinguishes them from the claim libraries:

> Research tools (such as gas chromatograph) are useful in the sense that they can be used in conjunction with other method steps to evaluate materials other than themselves. The claimed combinatorial libraries are not research tools in this sense. They are themselves the subject of basic research, whose usefulness or lack thereof has yet to be established. See id at page 4, example A.

There are several problems with the Examiner's analysis.

First of all, the claimed panels of peptide libraries <u>are</u> used to evaluate materials other than themselves. Once a peptide that binds a target protein is identified, it is used <u>as a reagent</u> in a screening of a "complementary library" (e.g., a benzodiazepine library). See page 18, lines 3-11. The desired drug is the benzodrazepine, etc., not the peptide. See page 6, lines 22-26, page 10, lines 27-32; page 11, lines 33-35, and pages 37-51, especially page 37, lines 22-27.

Secondly, the binding peptides have both an asserted and an obvious utility as binding reagents in assays. See, e.g., Ladner, USP 5,223,409, col. 105, lines 47-53. This utility does not require pharmacological activity. While it is certainly true that most of the peptides will not bind a given TP, it is equally reasonable to expect that <u>one or more will bind</u>.

The pragmatic proof of the practical utility of combinatorial libraries is that such libraries are commercially bought and sold, just like gas chromatographs.

Enclosed herewith are copies of pages 140-141 of the New

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England Biolabs catalogue. These show the commercial availability of the "Ph.D. Phage Display Peptide Library Kits" ($300 for 10 biopanning experiments) and the related "Ph.D. Peptide Display Cloning System", which are M13 pIII-based. Other commercial systems or vectors include Invitrogen's pFliTrx (display on E. coli flagella), Novagen's T7 Select Phage Display System (display on T7 phage); Display Systems Biotech's "display PHAGE System" (pIII-based), Stratagene's "SurfZap (pIII-based), and Invitrogen's pYD1 Yeast Display Vector Kit (yeast display). See generally Swanson, The Scientist, 13(6):__ (March 15, 1999), online at http://www.the-scientist.lib.upenn.edu/yr1999/mar/profile2_990315.html, "The Ties That Bind:Peptide Display Technology", and a page from the Invitrogen online catalogue, describing pYD1 Yeast Display Vector Kit.

Respectfully submitted,

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Enclosures
- Second Preliminary Amend. filed 9/29
- postcard receipt for the amendment
- postcard receipt for IDS filed 10/21/99
- pgs. 140-141 of the New England Biolabs catalogue
- Swanson (1999)
- Invitrogen catalogue page on pYD1

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(Nova) 1 of 1

APPLICANT(S): Fowlkes, et al.

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